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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,518	STEFFAN ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-77* is/are pending in the application.

4a) Of the above claim(s) *8-18,21-32,36-43,45-59 and 61-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20,33-35,44 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *8-77* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004 & 22 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 25 September 2006 to the claims has been entered in full. Claims1-7 have been canceled. New claims 67-77 have been added.

Election with traverse

2. Applicant's election with traverse of Group II, claims 19, 20, 33-35, 44 and 60, in the reply filed on 25 September 2006 is acknowledged.

3. The traversal is on the ground(s) that, SUMOylation blockers, deSUMOylation blockers, Ubiquitination activators and deUbiquitination inhibitors are inappropriately restricted under four inventions, as all these agents operate on small ubiquitin-related modifier-1 or SUMO-1 molecule. The Applicants further assert that the invention of the instant specification is directed to a method of treating neurodegeneration, which could be produced by any of the above agents, either by blocking SUMOylation or by enhancing deSUMOylation. As Inventions I-IV are directed to related processes, the Applicants suggest that the four inventions should rather be considered as four species. This is not found persuasive because Groups I-IV are restricted properly as they comprise patentably distinct inventions, wherein the methods of Group I-IV are distinct. As explained in the previous Office Action, page 3), although the four groups are related,

also emphasized by the Applicant, they are distinct inventions (See MPEP § 806.05(j)). Furthermore, Inventions I-IV are directed to methods that use different starting materials, follow different procedure and evaluation protocols, have distinct end-points and are not required one for the other. Specifically, the methods of Groups I-IV require administration of functionally and structurally different agents. Therefore, a search of all the four methods in one patent application would result in an undue search burden for the Examiner. The searches for the methods are not co-extensive, and the subject matter is divergent.

4. Furthermore, in order to have all four above-mentioned methods examined as one invention, in the response of 26 September 2006, the Applicants have cancelled claims 1-7 and attempted to withdraw claims 8-66, and introduced new set of claims (67-77), wherein the first claim (claim 67) is the broadest independent claim, linking all four agents mentioned above. However, as discussed above, Applicant's arguments are not persuasive and originally filed claims (19, 20, 33-35, 44 and 60) are considered by the Examiner in the instant application.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 8-18, 21-32, 36-43, 45-47, 49-51, 53-55, 57-59, 61-63 and 65-77 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 48, 52, 56 and 64 are withdrawn

from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species, there being no allowable generic or linking claim.

6. Applicant's election of Huntington's Disease as the species will be considered for examination. Applicant timely traversed the restriction (election) requirement in the reply filed on 25 September 2006.

7. Claims 19, 20, 33-35, 44 and 60, drawn to a method of treating neurodegeneration in a patient by administering a therapeutically effective amount of SUMOylation blocker, are being considered for examination in the instant application.

Sequence Compliance

8. The disclosure is objected to because of the following informalities: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Amino acid sequences for SV40 nuclear localization signal described in the specification do not have an associated SEQ ID number (pg 15, line 22). Additionally, the sequences in Figure 1A (dated 22 July 2004) are not associated with a relevant sequence identifier.

Appropriate correction is required.

Claim Objections

9. Claims 19-20, 33-34, 44 and 60 is objected to because of the following informalities:

10. Regarding claims 19-20, 33-34, 44 and 60, acronym "SUMO", recited should be spelled out for clarity.

11 Claims 19-20, 33-34 are missing the word "a" before "deSUMOylation enhancer"

Appropriate correction is required.

Claim Rejections - 35 USC § 112-Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 19, 20, 33-35, 44 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

13. The specification does not reasonably provide enablement for treating polyglutamine-expression-related and protein-aggregation related neurodegeneration, such as Huntington's disease, in a patient comprising

identifying such a patient at risk and administering a therapeutically effective amount of deSUMOylation enhancer, SUMO isopeptidase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

14. The claims are drawn to a method for treating polyglutamine-expression-related and protein aggregation related neurodegeneration, such as Huntington's disease, in a patient, comprising identifying such a patient at risk and administering a therapeutically effective amount of a deSUMOylation enhancer (SUMO isopeptidase).

15. The specification of the instant application teaches that long repeats of polyglutamine (polyQ) in specific disease genes results in neurodegenerative disorders, for example Huntington's Disease (page 12, lines 18-21). The specification also teaches that mutant proteins and/or pathogenic polyQ polypeptides form aggregates in the nucleus and cytoplasm of neurons in Huntington's Disease (page 1, lines 23-27). Further the specification teaches that a truncated portion of the mutant Huntingtin protein (Httex1p) causes Huntington's disease like disorder in mice and flies (page 12, lines 21-24). The specification further demonstrates that SUMOylation is a post-translational modification system in which SUMO-1 covalently attaches lysine residues and modifies protein function (page 2, lines 15-26). Additionally the specification suggests that preventing SUMOylation of proteins by deSUMOylation enhancers could

prove as potential treatments for neurodegenerative disorders. However, the specification does not disclose any methods or working examples to indicate a method for treating or identifying a patient at risk for polyQ-expansion-related neurodegeneration.

16. Undue experimentation would be required by one skilled in the art to identify "a patient at risk" for having the polyQ-expansion-related and protein-aggregation-related neurodegenerative disorder and treating patients with the above disorders (see claim 19, for example). Undue experimentation would also be required of the skilled artisan to identify and administer all possible deSUMOylation enhancers.

17. Relevant literature of the art teaches that SUMO, also called PIC1, Ubl1, sentrin, GMP1 etc., may function as an antagonist to ubiquitin and is useful in protein degradation (Melchoir F, Annu Rev Cell Dev Biol 16: 591-626, 2000, page 591; page 593). The art also teaches that SUMO-1 is a 101 amino acid polypeptide (Muller et al., Nature 2: 202-210). Muller et al., further teaches that SUMOylation is a reversible process, leading to deSUMOylation, wherein SUMO is excised from the target protein, a reaction catalyzed by isopeptidases (page 202-203, "SUMO deconjugation"). The prior art further teaches that four SUMO processing enzymes, having isopeptidase activity and belonging to a family of related proteins, have been characterized from humans and yeast (Melchoir et al. Annu. Rev. Cell Dev. Biol. 16: 591-626, 2000; see page 602, para 1). However, relevant literature does not teach identifying a patient at risk for

polyQ-related or protein-aggregation related neurodegenerative diseases and treating such patients with a deSUMOylation enhancer. Undue experimentation would also be required of one skilled in the art to treat all possible neurodegenerative diseases (claim 33), including all protein-aggregation related neurodegeneration by administration of any deSUMOylation enhancer. It is well known in the art that many neurodegenerative diseases are proven to be recalcitrant to treatment such as Alzheimer's Disease (Halliday et al Clin Exp Pharmacol Physiol 27: 1-8, 2000), Parkinson's Disease (Steece-Collier et al., PNAS USA 99(22): 13972-13974, 2002), Down's Syndrome (Appendix A), and Huntington's Disease (Feigin et al., Curr Opin Neurol 15: 483-489, 2002). Therefore, one skilled in the art would not be able to predict from the instant specification that all possible deSUMOylation enhancers, including SUMO isopeptidase, would be able to treat all neurodegenerative disorders, which have different pathophysiologies. Undue experimentation would be required to determine such.

18. Furthermore, the instant specification teaches the use of a Drosophila model for Huntington's Disease, which after crossing with the reduced function Drosophila SUMO mutant (*smt3*), results in the suppression of neurodegeneration (page 3, lines 24-27; page 27, lines 22-32; Figure 5A). The specification further demonstrates that decreased levels of SUMOylation results in the lowering of photoreceptor neuron degeneration in the fly model, induced by the Huntingtin gene (page 3,

lines 9-12); thereby suggesting that a reduction of SUMO-1 modification may prove to be useful for treatment of Huntington's disease. However, to test for treatment of a disease in a subject, one would need to conduct studies on non-human mammals that would more closely replicate the essential features of the pathophysiology of the disease in humans, as compared to invertebrate models. As Wang et al. (Acta Pharmacologica Sinica, 27(10): 1287-1302, 2006) suggests that the "proof of efficacy in mammalian models is considered a prerequisite before considering possible testing in humans" (page 1297, column 2, para 2). Wang et al., further teaches that since flies "are not accessible to externally administered drugs", the studies should be conducted in a mammalian model to get a better expression of the disease and "response to potential therapies" (see page 1295, column 1, para 2; page 1297, column 1, para 1). However, neither the specification of the instant application, nor the prior/post art literature teach any methods or working examples that indicate administration of any deSUMOylation enhancer for treatment in humans. As the molecular processes of pathogenesis of Huntington's disease are yet to be fully uncovered, the success of treatment or identifying such patient at risk would be unpredictable, thus the invention would entail undue experimentation by a skilled artisan.

19. Due to the large quantity of experimentation necessary to treat polyQ-expansion-related neurodegeneration by administration of a deSUMOylation enhancer, and identify such patient at risk; the lack of

direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which has yet to determine an ideal model for treatment of Huntington's Disease and, the unpredictability of using invertebrate models, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112-Written description

20. Claims 19, 33, 35, 44 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are also drawn to a method for treating polyglutamine-expression-related and protein aggregation related neurodegeneration, such as Huntington's disease, in a patient, comprising identifying such a patient at risk and administering a therapeutically effective amount of deSUMOylation enhancer, SUMO isopeptidase.

22. The specification of the instant application teaches that long repeats of polyglutamine (polyQ) in specific disease genes results in neurodegenerative disorders, for example Huntington's Disease (page 12,

lines 18-21). The specification also teaches that mutant proteins and/or pathogenic polyQ polypeptides form aggregates in the nucleus and cytoplasm of neurons in Huntington's Disease (page 1, lines 23-27). The specification further demonstrates that SUMOylation is a post-translational modification system in which SUMO-1 covalently attaches lysine residues and modifies protein function (page 2, lines 15-26). Additionally the specification suggests that preventing SUMOylation of proteins by deSUMOylation enhancers could prove as potential treatments for neurodegenerative disorders. However, the brief description in the specification describing the use of one example of deSUMOylation enhancer, does not comprise a representative number of species and hence is not adequate written description of an entire genus of deSUMOylation enhancers and methods using such. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, or any combination thereof. However, in this case, the specification has not shown a relationship between the structure, function, or properties of the claimed genus of deSUMOylation enhancers.

23. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art

that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

24. The skilled artisan cannot envision the deSUMOylation enhancers of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

25. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

26. Therefore, only SUMO isopeptidase, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claims 19-20, 33-35, 44 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

28. Claims 19-20, 33-35, 44 and 60 are indefinite because the claims do not have a step that clearly relates back to the preamble.

Conclusion

29. No claims are allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
October 25, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER